Molecular stages of rapid and uniform neuralization of human embryonic stem cells.

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Public Summary:

Scientific Abstract:
Insights into early human development are fundamental for our understanding of human biology. Efficient differentiation of human embryonic stem cells (hESCs) into neural precursor cells is critical for future cell-based therapies. Here, using defined conditions, we characterized a new method for rapid and uniform differentiation of hESCs into committed neural precursor cells (designated C-NPCs). Dynamic gene expression analysis identified several distinct stages of ESC neuralization and revealed functional modules of coregulated genes and pathways. The first wave of gene expression changes, likely corresponding to the transition through primitive ectoderm, started at day 3, preceding the formation of columnar neuroepithelial rosettes. The second wave started at day 5, coinciding with the formation of rosettes. The majority of C-NPCs were positive for both anterior and posterior markers of developing neuroepithelium. In culture, C-NPCs became electrophysiologically functional neurons; on transplantation into neonatal mouse brains, C-NPCs integrated into the cortex and olfactory bulb, acquiring appropriate neuronal morphologies and markers. Compared to rosette-NPCs,(1) C-NPCs exhibited limited in vitro expansion capacity and did not express potent oncogenes such as PLAG1 or RSPO3. Concordantly, we never detected tumors or excessive neural proliferation after transplantation of C-NPCs into mouse brains. In conclusion, our study provides a framework for future analysis of molecular signaling during ESC neuralization.